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Effectiveness of paliperidone long-acting injection in clinical practice.

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ABSTRACT

Background:
The aim of this study was to assess the clinical effectiveness of the long-acting injectable antipsychotic paliperidone palmitate using treatment continuation at one year as an outcome.

Methods:
Patients were initiated on paliperidone palmitate prior to December 2014 in a single health board in Wales (UK). Demographic factors which may have influenced outcome were analysed. For patients completing one year of treatment, inpatient stay in the 12 months prior to and following paliperidone palmitate initiation was compared.

Results:
Data were available for 64 patients, 41 had a diagnosis of schizophrenia and seven had previously received clozapine. Continuation rates at six and 12 months were 69% and 63% respectively. Treatment continuation was not associated with demographic factors. For continuers, mean inpatient stay prior to and post initiation was 83.2±105.3 and 73.5±103.3 days respectively ($p=0.61$). The most common reason for discontinuation was lack of effect ($n=9$).

Conclusions:
The proportion of patients remaining on treatment was comparable to that reported in other naturalistic studies. Prescribing for indications outside the product license was relatively common, although this did not appear to influence outcome. Treatment continuation at six months appeared to be a predictor of longer-term outcome.

Keywords:
Antipsychotic, paliperidone; long-acting injection; schizophrenia, effectiveness

Introduction:

Schizophrenia is a chronic, relapsing, severe mental illness associated with significant morbidity and mortality. The long-term management of schizophrenia may be limited by non-compliance with antipsychotic medication, which has been shown to be a significant factor in relapse and rehospitalisation (Ayuso-Gutierrez & del Rio Vega, 1997). Long-acting injectable formulations of antipsychotics (dopamine D_2 receptor antagonists or partial agonists) have been developed as a possible mechanism to address covert non-compliance, and may have some advantages over oral therapy in the management of this chronic relapsing condition (Alphs, et al., 2016). However, the influence of factors which might affect outcome, such as optimal dosing interval, remain to be fully investigated (Kisely, et al., 2015). Risperidone was the first of the newer, atypical antipsychotics to be formulated as a long-acting injection. Due to its pharmacokinetic properties, risperidone long-acting injection (RLAI) must be administered on a fortnightly basis (Eerdekens, et al., 2004). The active risperidone metabolite, 9-OH-risperidone, has been shown to have high affinity for the dopamine D_2 and serotonin 5-HT_{2A} receptors (Schotte, et al., 1996), and has been marketed as the atypical antipsychotic, paliperidone. A long acting injectable formulation of paliperidone as the palmitate salt received marketing authorisation (formerly known as the product licence) in the UK in 2011 and had the possible advantage of a pharmacokinetic profile which allowed monthly dosing (Samtani, et al., 2009).

The efficacy of paliperidone palmitate (PP) in the treatment of schizophrenia has been investigated in randomised controlled trials (RCTs). PP has shown evidence of benefit over placebo (Pandina, et al., 2010) and comparable efficacy and tolerability to RLAI (Pandina, et al., 2011). Whilst the methodology employed in RCTs allows assessment of the efficacy of interventions, such studies may not be generalizable to clinical practice. The strict inclusion and exclusion criteria result in participants being unrepresentative of real world patients. Moreover, short study durations may not be adequate to assess the long-term effectiveness of medicines intended for the treatment of chronic conditions (Stroup, et al., 2003).

Naturalistic observational studies (e.g (Attard, et al., 2014) (Deslandes, et al., 2015), and studies designed with pragmatic outcome measures such as treatment continuation (Stroup, et al., 2003) have provided evidence of the effectiveness of antipsychotics in settings more relevant to clinical situations. The aim of the present study was to assess the effectiveness of PP in a clinical setting using treatment continuation at one year as an outcome measure.

Methods:

Design

This was a retrospective, naturalistic, one year follow-up study of patients receiving PP in a single health board in Wales (UK), in both hospital inpatient and outpatient settings. For patients completing one year of treatment, a mirror-image comparison of hospital inpatient stay, in the 12 months prior to and following PP initiation was conducted. Data were collected from pharmacy records and by retrospective case-note review during November and December 2015. The health board quality improvement department and mental health clinical board approved the study.

Participants and outcome measures

All patients initiated on PP prior to December 2014 in a single health board in Wales were identified from pharmacy records and included in the study. Patients were classified as "continuers" (those completing 12 months on PP treatment), or "discontinuers" (those discontinuing within 12 months of initiation). Demographic factors which may have influenced treatment outcome including age at initiation, diagnosis (schizophrenia vs other indications including schizoaffective disorder), gender, previous antipsychotic, inpatient or outpatient status on initiation, prior clozapine treatment, two previous antipsychotic treatment failures and recreational drug use were recorded. The duration of hospital stay in the 12 months prior to and post PP initiation was used as a measure of treatment effectiveness in treatment continuers. For discontinuers, reasons for treatment discontinuation (as described in patient records), dose at discontinuation and the antipsychotic to which they were switched were

noted. Prior treatment with clozapine was considered an indication of treatment refractory illness.

Statistical analysis

Demographic factors which may have influenced treatment outcome were analysed using unpaired Student t-test for continuous variables and Fisher's Exact test for categorical data. The number of days spent as an inpatient prior to and following PP initiation was compared using paired Student t-test. All statistical analyses were conducted using GraphPad Prism version 6.0 (GraphPad Software, La Jolla, CA, USA).

Results:

Sixty-six patients received PP, of whom two moved abroad during the follow-up period and were lost to follow-up. Accordingly, one year outcome data were available for a total of 64 patients. Patient demographics are shown in table 1; 41 (36%) patients had a diagnosis of schizophrenia, the other common diagnoses were schizoaffective disorder (n=5; 8%), bipolar disorder (n=5; 8%) and persistent delusional disorder (n=4; 6%). Seven (11%) patients had previously received clozapine, and 49 (76%) were switched to PP from risperidone (either oral or long-acting injection). The proportion of patients remaining on treatment over time is shown in figure 1; forty (63%) patients remained on PP at one year.

Continuers

Treatment continuation (vs treatment discontinuation) was not associated with age at initiation (P=0.054 unpaired student t-test), diagnosis, gender, previous risperidone treatment vs other antipsychotic, inpatient/outpatient status on initiation, prior clozapine treatment, two previous treatment failures or recreational drug use (p=0.79; p=1.0; p=0.38; p=1.0; p=0.41; p=0.44 and p=0.43 respectively, Fisher's Exact test). In regard to patients completing one year on PP, the mean time spent as an inpatient in the 12 months prior to PP initiation was

83.2 ± 105.3 days, and in the 12 months post PP initiation it was 73.5 ± 103.3 days (p=0.61, paired student t-test).

Discontinuers

Twenty-four patients discontinued PP within one year, 12 of whom discontinued between 90 and 120 days and four of whom discontinued between 120 and 365 days (see figure 1). Mean dose at discontinuation, reasons for discontinuation and antipsychotic treatment post discontinuation are shown in table 2. The most common reason for discontinuation was perceived lack of effect (n=9). The doses at discontinuation for these patients were 100mg (n=4) and 150mg (n=5), (mean=127.8mg), and the antipsychotics prescribed post PP were clozapine (n=7), flupenthixol decanoate (n=1) and amisulpride (n=1). Seven patients discontinued due to adverse effects, which encompassed weight gain (n=2), extra-pyramidal side effect (n=2), sexual dysfunction (n=2) and sedation (n=1). Of the five patients switching from risperidone to PP due to a lack of effect, 3 had discontinued PP at one year due to lack of effect (the other two patients continued on PP treatment).

Discussion:

This study assessed the effectiveness of PP in clinical practice using treatment continuation at 12 months as an outcome measure. Of the 64 patients who were included in the study, 40 (63%) remained on treatment (classified as “continuers”) at one year. There were no significant differences in demographic factors between continuers and patients discontinuing PP, therefore baseline characteristics did not appear to influence treatment outcome in this study. The majority (83%) of patients who discontinued treatment did so within the first 180 days, therefore completion of six months treatment appeared to be a good indicator of continuation at one year. In the case of treatment continuers, there was no significant difference in inpatient stay in the 12 months prior to and post PP initiation. The most common reason for treatment discontinuation was lack of effect.

The proportion of patients remaining on treatment was comparable to the 65% (Attard, et al., 2014) and 60% (Whale, et al., 2015) reported in similar one-year naturalistic studies of PP. One study comparing the outcomes of patients treated with PP, RLAI and zuclopentixol decanoate reported a somewhat lower continuation rate of PP (48%), albeit over a longer 18 month follow-up period (Cordiner, et al., 2016). Continuation with PP was noticeably higher than that seen at the same time point in a similar study of RLAI (45%) in our health board (Deslandes, et al., 2009) and that observed in another study of RLAI in the UK (Taylor, et al., 2009). However, it must be noted that the observational nature of these studies does not allow direct comparisons to be made. In the case of continuers, there was no significant difference in the number of days spent as an inpatient in the 12 months prior to and following PP initiation. This was in contrast to other similar naturalistic studies of PP which revealed a reduction in hospital admissions and inpatient stay post initiation in hospital in the UK (Taylor, et al., 2016) (Nikolic, et al., 2017) albeit over longer periods (two and three years post PP initiation respectively) than seen in our study. Two one year mirror image studies, one from Canada (Vincent, et al., 2017) and one from the UK (Bressington, et al., 2015), showed a non-significant reduction in hospitalisation days when using first PP injection as the mirror point, suggesting that study duration may be an important factor when measuring this outcome.

None of the demographic factors analysed in this study appeared to influence treatment outcome. This was in contrast to the findings of other studies of PP which found that outpatient status on initiation, switching from risperidone (Attard, et al., 2014) and a diagnosis of schizophrenia (Whale, et al., 2015) were associated with treatment continuation at one year. Similarly, outpatient initiation and switching from risperidone have also been shown to predict PP continuation at two years (Taylor, et al., 2016). The relatively small number of subjects in our study may be an explanation for these differences. Prescribing for indications outside of the marketing authorisation accounted for 36% of patients in our study. In part, this may reflect the more limited indications of the long-acting injectable paliperidone

preparation compared to the oral equivalent. However, it also highlights the relatively common phenomenon of off-label prescribing within the field of psychiatry. Nevertheless, patients treated for conditions other than schizophrenia were no more likely to discontinue at one year, providing some evidence for the effectiveness of PP in this group. Although demographic factors were not associated with outcome, treatment continuation at six months appeared to be conducive to or suggestive of continuation at one year. The majority (83%) of patients who discontinued PP did so within six months of treatment initiation, whilst 91% of those completing six months went on to complete one year. This was largely in accordance with a more long-term finding that completion of one year of treatment with RLAI or oral aripiprazole was an indicator of subsequent continuation at five years in a natuaralistic cohort (Deslandes, et al., 2015). A perceived lack of effect was the most common reason for discontinuation, consistent with other naturalistic studies (Attard, et al., 2014) (Whale, et al., 2015) (Cordiner, et al., 2016) and accounted for 14% of the total sample. Despite lack of effect being the reason for discontinuation, 4/9 (56%) of these patients did not receive the maximum licensed dose of PP (150mg), whilst 3/9 (33%) had previously been treated with clozapine. Therefore 6/9 individuals might have been expected to experience a poor response due to sub-optimal dosing or a history of treatment refractory illness. PP appeared to have similar tolerability to that seen in our previous study of RLAI with seven (11%) of the 64 patients discontinuing due to adverse effects, compared with 10% reported by (Deslandes, et al., 2009). In this context, other naturalistic studies of PP have reported both lower (5%) (Attard, et al., 2014) and slightly higher (13%) (Cordiner, et al., 2016) levels of discontinuation due to adverse effects.

Patient choice was the reason for PP initiation in 16 patients, 14 of whom chose PP on the basis of monthly rather than fortnightly dosing when switching from RLAI. However, this did not appear to influence outcome, with similar proportions of both continuers and discontinuers (25%) switching to PP for this reason. Furthermore, of the six of these patients who subsequently discontinued, three did so due to refusal of PP. Despite the chemical and

pharmacological similarities between paliperidone and risperidone, five patients switched to PP from oral risperidone or RLAI due to lack of effect. The rationale for this was the higher licensed dose equivalence of PP (150mg/month) compared with RLAI (100mg/month). This did not appear to influence outcome however, with three of the five patients subsequently discontinuing PP due to lack of effect. Across the whole study cohort the mean PP dose at end point was only slightly greater than 100mg, however approximately 30% of continuers received 150mg and therefore a higher equivalent dose than could have been achieved within the RLAI license.

This was a retrospective, naturalistic, observational study, and the methodological limitations were common to many such studies. There was no comparator group, no formal assessment of mental state nor randomisation, therefore any conclusions must be treated with a degree of caution. However, the study does report outcomes in real world patients (many of which would have been excluded from RCTs), being treated for both licensed and unlicensed indications and with an extended period of follow-up. PP appeared to show equivalent effectiveness in both schizophrenia and other indications. This may offer some reassurance to prescribers given the relatively common use of PP for indications outside the product license. However, it must be noted that the study was not designed to compare the outcomes of these two groups, and possible differences in the populations do not allow direct comparisons to be performed. Although the overall continuation rate seen in this study was only 63%, the subsequent completion rate for those who remained on treatment at six months (91%) was encouraging and suggested that outcome at six months may be a useful indicator of longer-term treatment continuation.

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Table 1. Patient demographics, reasons for initiation and dose at study endpoint.

	All patients (n=64)	Continuers (n=40)	Discontinuers (n=24)
Age at initiation, yrs			
Mean ± sd	43.8 ± 15.3	46.6 ± 15.7	39.0 ± 13.6
Range	18–78	21–78	18–78
Gender, n (%)			
Male	45 (70)	28 (70)	17 (71)
Previous clozapine, n (%)	7 (11)	3 (8)	4 (17)
2 previous treatment failures, n (%)	38 (59)	22 (55)	16 (67)
Indication, n (%)			
Schizophrenia	41 (64)	25 (63)	16 (67)
Other	23 (36)	15 (38)	8 (33)
Inpatient on initiation, n (%)	39 (61)	24 (60)	15 (63)
Recreational drug use, n (%)	23 (36)	16 (40)	7 (29)
Switched from, n (%)			
Risperidone po	20 (31)	11 (28)	9 (38)
Risperidone IM	29 (45)	18 (45)	11 (46)
Other antipsychotic	15 (23)	11 (28)	4 (17)
Reason for initiation, n (%)			
Previous non-compliance	30 (47)	20 (50)	10 (42)
Patient choice	16 (25)	10 (25)	6 (25)
Previous poor response	13 (20)	7 (18)	6 (25)
Previous side effect	5 (8)	3 (8)	2 (8)
Dose at end point, mg/month			
Mean ± sd	109.4 ± 33.2	107.5 ± 33.6	112.5 ± 33.0
Range	50–150	50–150	50–150

Table 2. Reasons for discontinuation and antipsychotic post PP

	All discontinuers (n=24)	Previous clozapine (n=4)	Previous non-clozapine (n=20)
Dose at discontinuation, mg			
Mean ± sd	112.5 ± 33.0	125.0 ± 28.9	110.0 ± 33.8
Range	50–150	100–150	50–150
Reason for discontinuation, n (%)			
Lack of effect	9 (38)	3 (75)	6 (30)
Side effect	7 (29)	1 (25)	6 (30)
Patient refused	4 (17)	–	4 (20)
Patient choice	3 (13)	–	3 (15)
Patient death	1 (4)	–	1 (5)
Switched to, n (%)			
Clozapine	9 (38)	2 (50)	7 (35)
Atypical po (not clozapine)	5 (21)	–	5 (25)
Atypical IM	3 (13)	1 (25)	2 (10)
Typical IM	1 (4)	1 (25)	–
No antipsychotic	6 (25)	–	6 (30)

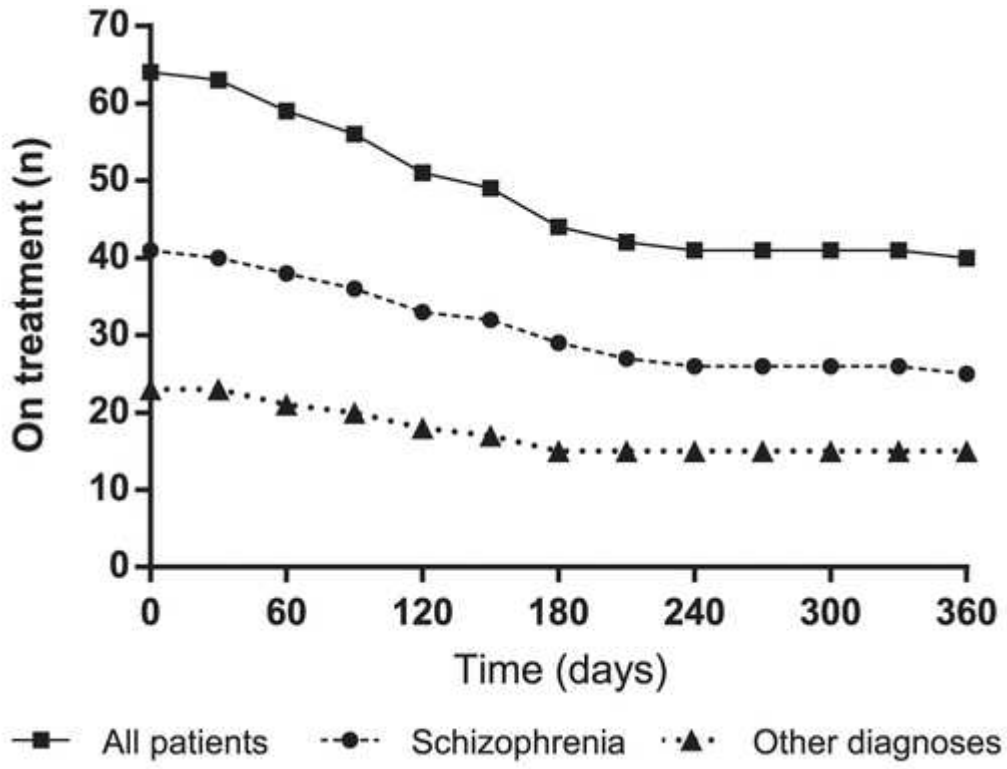

Figure 1. Percentage of patients remaining on treatment over time; grouped according to whether they had received previous clozapine treatment (PC) or had not received previous clozapine treatment (non PC)